

# CAVELIER

ABOGADOS

www.cavelier.com  
cavelier@cavelier.com

EDIFICIO SISKI  
CARRERA 4 No. 72 - 35  
BOGOTÁ 8, COLOMBIA

Teléfono: (57-1) 347 3611  
Telefax: (57-1) 211 8650  
(57-1) 700 4814  
Fax in U.S.A.: (1-305) 675 7743

Señor Director

## DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-082396-00006-0000

Fecha: 2011-12-28 11:31:05 Dep. 2020 DIR.NUEVASCR  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 449 RESPUESOPOSICI Folios: 41

Trámite : 011 Evento : 378 Actuación : 449

Referencia : Expediente No. 09.082.396  
Asunto : Solicitud de patente para SAL DE NAPADISILATO  
DE 5-(2-{[6-(2,2-DIFLUORO-2-FENILETOXI)  
HEXIL]AMINO}-1-HIDROXIETIL)-8-  
HIDROXIQUINOLIN-2(1H)-ONA COMO AGONISTA DEL  
RECEPTOR ADRENÉRGICO β2  
Solicitante : ALMIRALL, S.A.  
Opositor : LABORATORIO FRANCO COLOMBIANO S.A. LAFRANCOL  
S.A.

### I. ALEGATOS CONTESTACIÓN OPOSICIÓN

Yo, Luz Clemencia de Páez, en mi condición de apoderada de la sociedad solicitante ALMIRALL S.A., por el presente escrito doy respuesta dentro de la prórroga solicitada a la oposición formulada por el doctor Tito Noé PARRA MURILLO, apoderado de la sociedad LABORATORIO FRANCO COLOMBIANO S.A. LAFRANCOL S.A. contra la solicitud de patente para la invención denominada SAL DE NAPADISILATO DE 5-(2-{[6-(2,2-DIFLUORO-2-FENILETOXI) HEXIL]AMINO}-1-HIDROXIETIL)-8-HIDROXIQUINOLIN-2(1H)-ONA COMO AGONISTA DEL RECEPTOR ADRENÉRGICO β2 que se tramita en el expediente de la referencia.

## **II. CONTESTACIÓN DENTRO DEL TÉRMINO LEGAL**

El Oficio N° 10864, que dispone el traslado de la oposición formulada fue notificado por fijación en lista el 14 de julio de 2011, por lo que el término de la prórroga solicitada vence el 6 de enero de 2012; de manera que la oposición está siendo contestada en término legal.

## **III. RESPUESTA A LA PETICIÓN**

Me opongo a la pretensión de la sociedad LAFRANCOL S.A., y en consecuencia solicito se declare infundada la oposición presentada en su nombre y se otorgue la patente para la invención denominada SAL DE NAPADISILATO DE 5-(2-{[6-(2,2-DIFLUORO-2-FENILETOXI) HEXIL]AMINO}-1-HIDROXIETIL)-8-HIDROXIQUINOLIN-2(1H)-ONA COMO AGONISTA DEL RECEPTOR ADRENÉRGICO  $\beta$ 2 solicitada por mi representada la sociedad ALMIRALL, S.A. que se tramita bajo el expediente No. 09.082.396.

## **IV. FUNDAMENTO FÁCTICO DE LA OPOSICIÓN**

Fundamenta el apoderado de la sociedad opositora su pretensión en los siguientes argumentos principales:

- 4.1. La invención solicitada carece de los requisitos de NOVEDAD, NIVEL INVENTIVO y APLICACIÓN INDUSTRIAL, por lo tanto no puede ser objeto de patente.
- 4.2. Lo anterior, toda vez que involucra moléculas que son mundialmente conocidas tales como Dexametasona, Dudesonida, Ciclesonida, Betametasona, entre otras.
- 4.3. Como fundamento de sus alegaciones se citan los siguientes documentos:

|                     |                 |      |
|---------------------|-----------------|------|
| <b>DEXAMETASONA</b> | The Merck Index |      |
|                     | US 3007923      | 1961 |
|                     | DE 1113690      | 1961 |
|                     | GB 869511       | 1960 |
| <b>BUDESONIDA</b>   | DE 2323215      | 1973 |
|                     | US 3929768      | 1975 |
| <b>CICLESONIDA</b>  | DE 4129535      | 1992 |
|                     | US 5482934      | 1996 |
| <b>BETAMETASONA</b> | US 3053865      | 1962 |
|                     | US 3104246      | 1963 |

4.4. De acuerdo con lo anterior se concluye que la invención solicitada no es objeto de patente ya que pretende proteger "objetos que no son considerados invenciones."

#### **V. RESPUESTA A LOS HECHOS Y ALEGATOS**

A continuación me permito presentar a consideración de este Despacho, las razones que demuestran la falta de fundamento fáctico y jurídico de la oposición formulada a nombre de la sociedad LAFRANCOL S.A. y la improcedencia de su pretensión para que sea negada la patente para la invención identificada en la referencia.

5.1. Señala el apoderado de la sociedad opositora, que la invención solicitada por mi representada carece de los requisitos establecidos en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina para que se le otorgue el privilegio de patente, esto es, NOVEDAD, NIVEL INVENTIVO y APLICACIÓN INDUSTRIAL.

5.2. Sin embargo, no se señalan los hechos que de manera clara y contundente permiten demostrar que la invención de mi representada carece de estos requisitos.

5.3. Precisamente la misma Decisión 486 define en sus artículos 16, 18 y 19 cuáles son los presupuestos que permiten determinar cuando una invención tiene NOVEDAD, NIVEL INVENTIVO y APLICACIÓN INDUSTRIAL, en los siguientes términos:

**“Artículo 16.-** Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.

[...]

**Artículo 18.-** Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.

**Artículo 19.-** Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios.”  
-subrayado fuera de texto-

5.4. Para el presente caso se tiene, por un lado, que el apoderado de la parte opositora simplemente se ha limitado a enumerar una lista de documentos, sin indicar cuál es el efectivamente relevante para el estudio de novedad o nivel inventivo por tratarse del documento más cercano del estado del arte.

De otro lado, no ha efectuado un análisis de fondo sobre los documentos citados frente a la invención de mi representada, que

## ABOGADOS

permita llevar al examinador al convencimiento que realmente la invención solicitada en este expediente carece de los requisitos de patentabilidad mencionados.

5.5. Precisamente siguiendo los lineamientos de los artículos 16 y 18 de la Decisión 486 se tiene que:

- una invención se considera novedosa si provee por lo menos una diferencia técnica con respecto al estado del arte más cercano; y
- una invención posee nivel inventivo si no puede ser derivada de manera obvia a partir del arte previo y/o si provee mejoras o un efecto inesperado sobre dicho arte previo

5.6. Ciertamente para la evaluación de la novedad y el nivel inventivo respectivamente, se deben señalar los documentos más cercanos del estado del arte en los cuales se revela explícitamente todas las características técnicas de la invención y/o revelan sugerencias y enseñanzas claras para el técnico en la materia que lo lleven a obtener la invención objeto de oposición.

5.7. Así entonces, se debe concluir que para que pudieran ser consideradas pertinentes las alegaciones de la parte opositora en cuanto a la ausencia de novedad y nivel inventivo de la presente invención, su apoderado ha debido haber señalado con claridad y sin lugar a dudas los apartes de los documentos más cercanos del estado del arte, donde se revele la composición que es objeto de la presente solicitud de patente, y/o por lo menos señalar las enseñanzas que de dichos documentos revelarían al técnico que de manera obvia y evidente se hubiera podido llegar a la invención solicitada por mi poderdante en este asunto.

5.8. En efecto, una oposición debidamente fundamentada no debe basarse simplemente en apreciaciones personales, sino que toda objeción respecto a la falta de novedad, nivel inventivo y además de la

## ABOGADOS

aplicación industrial debe ser probada. En particular, el opositor tiene la carga de demostrar a partir de lo revelado en el estado del arte que la invención en su integridad ya se encontraba allí revelada, que una persona versada en la materia habría propuesto las características técnicas que distinguen la invención reivindicada y que permiten alcanzar los resultados obtenidos por la misma, y que además, a la luz de lo establecido en el artículo 19 de la Decisión 486, la invención no puede ser producida o utilizada en cualquier tipo de industria.

5.9. Ahora bien, el hecho de que el apoderado de la sociedad opositora se limite a listar una serie de documentos en que se divulgan algunas "moléculas" que hacen parte de la composición reivindicada en la presente solicitud, no es idóneo ni conducente para demostrar la ausencia de los requisitos de patentabilidad que se mencionan en este escrito, toda vez que es necesario resaltar que la invención reivindicada tiene que considerarse en su conjunto, que la misma consiste en una combinación de elementos cuya unidad presenta características técnicas específicas y que la misma constituye un paso adelante en lo existente en el estado de la técnica.

5.10. Así, se hace necesario poner de presente que la novedad no es un requisito que deba cumplir cada uno de los componentes que conforman la invención, puesto que incluso al ser conocidos individualmente, las composiciones específicas entre ellos pueden dar lugar a una combinación que no había sido anticipada en el estado del arte y que adicionalmente solucione un problema técnico, como sucede en el presente caso.

5.11. Para el presente se tiene que todos los documentos citados en el escrito de oposición se refieren a compuestos que son: dexametasona, budesonida, ciclesonida y betametasona, que pertenecen al grupo de los corticosteroides; por su parte, la invención solicitada se refiere a la sal napadisilato de 5-(2-([6-(2,2-difluoro-2-feniletoksi) hexil]amino)-1-hidroxietil)-8-hidroxiquinolin-2(1H)-ona; esta claro que este

**ABOGADOS**

compuesto es diferente de los compuestos citados por la oposición y por lo tanto la presente invención presenta novedad frente a los compuestos arriba mencionados.

Queda claro entonces que no se demostró que la invención solicitada por mi representada adolezca del requisito de NOVEDAD frente a los documentos citados como fundamento de la oposición.

5.12. Adicionalmente, es pertinente destacar que invención también presenta actividad inventiva respecto a todos los documentos citados por la oposición ya que todos estos compuestos pertenecen al grupo de los corticosteroides en cambio el compuesto de la presente invención es un agonista beta2 que es un mecanismo de acción totalmente distinto a los corticosteroides.

Por otro lado, cabe destacar que la estructura química del compuesto de la presente invención es totalmente distinta y muy alejada a las estructuras de los corticosteroides mencionados por la oposición y por lo tanto queda muy evidente que un experto en la materia nunca jamás hubiera llegado a la estructura química del compuesto de la presente invención partiendo de los compuestos mencionados.

5.13. De este modo, es claro que los documentos citados por el apoderado de la sociedad LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. tampoco son relevantes para el estudio del nivel inventivo de la presente solicitud, y adicionalmente dichos documentos no presentan enseñanza o sugerencia alguna que lleve de manera obvia y evidente obtener como resultado la invención aquí solicitada.

5.14. Por último, es evidente que la presente invención tiene aplicación industrial ya que se trata de un compuesto útil en el tratamiento de enfermedades respiratorias.

5.15. En consecuencia, se puede concluir sin lugar a dudas que al no haber sido demostrado por el apoderado de la sociedad opositora que la

## ABOGADOS

invención solicitada por mi poderdante realmente carece de los requisitos de NOVEDAD, NIVEL INVENTIVO y APLICACIÓN INDUSTRIAL su pretensión no tiene vocación de prosperar, por lo que procede declarar infundada la oposición formulada y proseguir con el estudio de fondo de la solicitud como consecuencia de la solicitud de examen de patentabilidad oportunamente presentada en este asunto.

## VI. PETICIONES

Por los anteriores hechos, solicito respetuosamente a este Despacho proceder a:

6.1. Declarar **infundada la oposición** presentada a nombre de la sociedad LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

6.2. Proseguir con el estudio de fondo de la solicitud como consecuencia del examen de patentabilidad oportunamente solicitado, y

6.3. Conceder la patente para la invención denominada SAL DE NAPADISILATO DE 5-(2-{[6-(2,2-DIFLUORO-2-FENILETOXI) HEXIL]AMINO}-1-HIDROXIETIL)-8-HIDROXIQUINOLIN-2(1H)-ONA COMO AGONISTA DEL RECEPTOR ADRENÉRGICO  $\beta_2$  en favor de mi representada la sociedad ALMIRALL, S.A., por cumplir con los requisitos previstos en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina.

## VII. PRUEBAS

Comendidamente solicito se tengan como pruebas en este asunto, todos y cada uno de los documentos que obran en el expediente de la referencia, y adicionalmente las siguientes:

**ABOGADOS**

7.1. Copia del informe de búsqueda internacional que reconoce la patentabilidad de la invención solicitada por mi representada en este asunto.

7.2. Copia de la comunicación por la cual la Oficina Europea de Patentes ha emitido su intención de conceder la patente para la invención solicitada, junto con la copia del texto propuesto para la concesión.

**VIII. NOTIFICACIONES**

Mi representada y yo recibiremos notificaciones en la Secretaría de su Despacho o en mi oficina de abogado ubicada en la carrera 4ª N° 72 - 35 de esta ciudad de Bogotá, D.C.

Señor Director,

  
**LUZ CLEMENCIA DE PAEZ**  
C.C. 35.456.344 de Usaquén  
T.P.A. No. 23.555

COLO-17153-841-001-9  
COLO-17153-264-002-5  
SCT\SCT\ID-207398\WPC17153  
No. M-2011-207398\SCT



European Patent Office  
80298 MUNICH  
GERMANY  
Tel: +49 89 2399 0  
Fax: +49 89 2399 4465



Srinivasan, Ravi Chandran  
J.A. Kemp & Co.  
14 South Square  
Gray's Inn  
London WC1R 5JJ  
ROYAUME-UNI

Formalities Officer  
Name: Siefert, Alexandra  
Tel: +49 89 2399 - 2469  
or call  
+31 (0)70 340 45 00

|                                        |                        |                    |
|----------------------------------------|------------------------|--------------------|
| Application No.<br>08 707 620.4 - 2117 | Ref.<br>N.103886A RCS/ | Date<br>19.07.2011 |
| Applicant<br>Almirall, S.A.            |                        |                    |

#### Communication under Rule 71(3) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

#### In the text for the Contracting States:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE  
SI SK TR

#### Description, Pages

|                          |                             |            |
|--------------------------|-----------------------------|------------|
| 1, 2, 4, 5, 8-18, 20, 21 | as originally filed         |            |
| 3, 6, 7, 19              | filed in electronic form on | 06-06-2011 |

#### Claims, Numbers

|      |                             |            |
|------|-----------------------------|------------|
| 1-17 | filed in electronic form on | 06-06-2011 |
|------|-----------------------------|------------|

#### Drawings, Sheets

|         |                     |
|---------|---------------------|
| 1/3-3/3 | as originally filed |
|---------|---------------------|

#### With the following amendments to the above-mentioned documents by the division

|                 |     |
|-----------------|-----|
| Claims, Numbers | 17* |
|-----------------|-----|

#### Comments

\*: claim 17 was modified in order to reflect the dependency on the purpose limited product claim 16

A copy of the relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within a non-extendable period of **four months** of notification of this communication

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

EUR

2. to pay the fee for grant and publishing;

Reference 007 830.00

3. to pay the additional claims fee(s) (Rule 71(6) EPC)  
number of claims fees payable: 2

Reference 016 420.00

Total amount 1250.00

The mention of the grant of the patent shall be published in the European Patent Bulletin as soon as possible after the requirements concerning the translation of the claims and the payment of the fees for grant and publishing, claims fees, designation fee and renewal fees as laid down in Rule 71(3), (4), (6) and (8) and (9) EPC are fulfilled.

If you do not approve the text intended for grant but wish to request amendments or corrections, the procedure described in Rule 71(4) EPC is to be followed.

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

If this communication is based upon an auxiliary request, and you reply within the time limit set that you maintain the main or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the enclosed claims contain amendments proposed by the Examining Division, and you reply within the time limit set that you cannot accept these amendments, refusal of the application under Article 97(2) EPC will result if agreement cannot be reached on the text for grant.

In all cases except those of the previous two paragraphs, if the fees for grant and publishing or claims fees are not paid, or the translations are not filed, in due time, the European patent application will be deemed to be withdrawn (R. 71(7) EPC).

For all payments you are requested to use EPO Form 1010 or EPO Form 1010E or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO publication server <https://data.epo.org/publication-server/> or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent **together with one copy** of the patent specification provided that the request is filed within the time limit of Rule 71(3) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 71(3) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 71(3) EPC time limit, the certificate will be delivered without a copy of the patent specification (R.74 EPC, Decision of the President of the EPO, Special edition No.3, OJ EPO 2007, D.2).

#### **Filing of a divisional application**

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and shall be in the language of the proceedings relating to the present application (cf. Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending and the time limit for filing divisional applications must be observed (Rule 36(1) EPC; Guidelines for Examination in the EPO, A-IV, 1.1.1).

#### **Note on payment of renewal fees**

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71(9) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

#### **Filing of translations in the Contracting States**

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office

[www.epo.org](http://www.epo.org) → Patents → Law → Legal texts → National law relating to the EPC

[www.epo.org](http://www.epo.org) → Patents → Law → Legal texts → London Agreement

#### **In case of a valid extension**

As regards translation requirements prescribed by the Extension States, please consult the website of the European Patent Office

[www.epo.org](http://www.epo.org) → Patents → Law → Legal texts → National law relating to the EPC

**Failure to supply a prescribed translation in a Contracting State or an Extension State may result in the patent being deemed to be void *ab initio* in the State concerned (Article 65(3) EPC).**

#### **Important note to users of the automatic debiting procedure**

The fees for grant and publishing and also any additional claims fees due under Rule 71(6) EPC will be debited automatically on the date of filing of the translation of the (relevant) claims, or on the last day of the period of this communication. However, if the designation fee becomes due as set out in Rule 71(8) EPC and/or a renewal fee becomes due as set out in Rule 71(9) EPC, these should be paid separately by another permitted means of payment in order not to delay the publication of the mention of grant. The same applies in these circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying Information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplement to OJ EPO 3/2009).

**Examining Division:**

|                      |                     |
|----------------------|---------------------|
| <b>Chairman:</b>     | Weisbrod, Thomas    |
| <b>2nd Examiner:</b> | Bader, Karl Günther |
| <b>1st Examiner:</b> | Moriggi, J          |



Siefert, Alexandra  
**For the Examining Division**  
Tel. No.: +49 89 2399 - 2469

Enclosure(s):      Form 2056  
                         28 Copies of the relevant documents

~~NAPADISYLATE SALT OF 5-(2-([6-(2,2-DIFLUORO-2-PHENYLETHOXY)-~~  
~~HEXYL]AMINO)-1-HYDROXYETHYL)-8-HYDROXYQUINOLIN-2(1H)-ONE AS~~  
~~AGONIST OF THE  $\beta$ 2 ADRENERGIC RECEPTOR~~

## FIELD OF THE INVENTION

The present invention is directed to novel crystalline naphthalene-1,5-disulfonic acid salts (napadisylates) of 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one, its enantiomers and solvates thereof. The invention is also directed to pharmaceutical compositions comprising the crystalline salts, methods of using them to treat respiratory diseases associated with  $\beta$ 2 adrenergic receptor activity, and processes and intermediates useful for preparing such salts.

## BACKGROUND OF THE INVENTION

$\beta$ 2 adrenergic receptor agonists are advantageously administered directly into the respiratory tract by inhalation when used for treating pulmonary or respiratory disorders. Several types of pharmaceutical inhalation devices have been developed for administering therapeutic agents by inhalation including dry powder inhalers (DPI), metered-dose inhalers (MDI) and nebulizer inhalers. It is highly desirable to have a crystalline form of the  $\beta$ 2 adrenergic receptor agonists that is neither hygroscopic nor deliquescent and which has a relatively high melting point thereby allowing the material to be micronized without significant decomposition or loss of crystallinity to prepare the pharmaceutical compositions and formulations for use in such devices.

5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one is claimed and described in published patent application WO 2006/122788 A1.

Although the 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one has shown adequate pharmacological behaviour it has proved difficult to obtain it in the form of a salt which is crystalline, not hygroscopic nor deliquescent and which has a relatively high melting point to enable micronization.

So far no crystalline salt of 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one having the desired properties has been reported.

- 5 Accordingly, a need exists for stable, non-deliquescent salt forms of this compound which has acceptable levels of hygroscopicity and relatively high melting points.

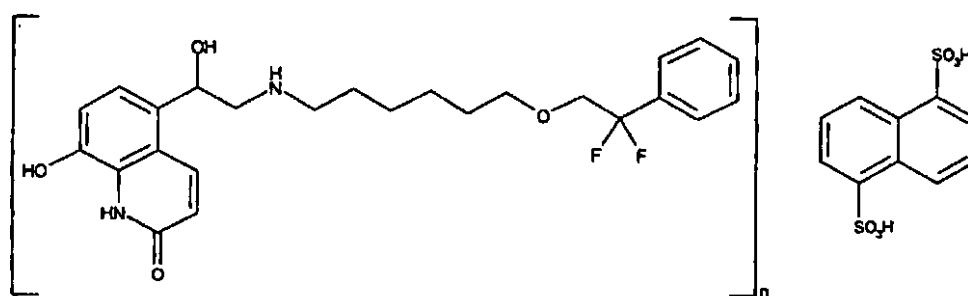
#### SUMMARY OF THE INVENTION

- 10 It has now been found that naphthalene-1,5-disulfonic acid salts of 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one can be obtained in a crystalline form which is neither hygroscopic nor deliquescent and which has a relatively high melting point thereby allowing the material to be micronized without significant decomposition or loss of crystallinity.

15

The present invention provides a crystalline mononapadisylate and/or heminapadisylate salt of 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one and pharmaceutically acceptable solvates thereof.

- 20 Typically, the crystalline naphthalene-1,5-disulfonic acid salts of the invention have the formula (I):



(I)

wherein *n* has a value of 1 or 2.

25

The present invention particularly provides the crystalline salt as a mononapadisylate salt or as a heminapadisylate salt and solvates thereof.

The invention also provides a pharmaceutical composition comprising a salt of the invention and a pharmaceutically-acceptable carrier. The invention further provides combinations comprising a salt of the invention and one or more other therapeutic agents  
5 and pharmaceutical compositions comprising such combinations.

~~The invention~~ also provides a method of treating a pulmonary disease or condition associated with  $\beta$ 2 adrenergic receptor activity such as asthma or chronic obstructive pulmonary disease, in a mammal, comprising administering to the mammal, a  
10 therapeutically effective amount of a salt of the invention. The invention further provides a method of treatment comprising administering a therapeutically effective amount of a ~~combination of a salt of the invention together with one or more other therapeutic agents~~

The invention further provides synthetic processes and intermediates described herein,  
15 which are useful for preparing salts of the invention.

The invention also provides a salt of the invention as described herein for use in ~~medical therapy, as well as the use of a salt of the invention in the manufacture of a formulation or~~  
~~medicament for treating a pulmonary disease or condition associated with  $\beta$ 2 adrenergic~~  
20 ~~receptor activity such as~~ asthma or chronic obstructive pulmonary disease in a mammal.

#### BRIEF DESCRIPTION OF FIGURES

Figure 1 shows the X-Ray Powder Diffraction (XRPD) pattern of 5-(2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one  
25 heminapadisylate. The figures on the Y axis are intensity (counts). The figures on the X axis show 2 Theta ( $^{\circ}$ ).

Figure 2 shows the DSC pattern of 5-(2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate. The figures on the Y axis  
30 are energy (W). The figures on the X axis are temperature ( $^{\circ}$ C).

Figure 3 shows the TGA pattern of 5-(2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate. The figures on the Y axis are weight (%). The figures on the X axis are temperature (°C).

5

#### DETAILED DESCRIPTION OF THE INVENTION

When describing the salts, compositions and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

10

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human patient which includes:

15

(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

20

(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;

(c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

25

(d) alleviating the symptoms of the disease or medical condition in a patient.

The phrase "pulmonary disease or condition associated with  $\beta$ 2 adrenergic receptor activity" includes all pulmonary disease states and/or conditions that are acknowledged now, or that are found in the future, to be associated with  $\beta$ 2 adrenergic receptor activity.

Such disease states include, but are not limited to asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema).

5 The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, i.e. a salt of the invention or a pharmaceutically-acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include by way of example, water, ethanol, isopropanol and the like. When the solvent is water, the solvate formed is a hydrate.

10

It will be appreciated that the term "or solvate or stereoisomer thereof" is intended to include all permutations of solvates and stereoisomers, such as a solvate of a stereoisomer of a salt of formula (I).

15 The salts of the invention contain a chiral center. Accordingly, the invention includes racemic mixtures, enantiomers, and mixtures enriched in one of the enantiomers. The scope of the invention as described and claimed encompasses the racemic forms of the salts as well as the individual enantiomers and enantiomer-enriched mixtures.

20 Of particular interest are the salts:

(*R,S*) 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one, napadisylate

25 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(*R*)-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one, napadisylate

(*R,S*) 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate

5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(*R*)-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate

30

and pharmaceutically acceptable solvates thereof.

Of outstanding interest are the salts:

- 6 -

(R,S) 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one, heminapadisylate  
5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one, heminapadisylate

and pharmaceutically acceptable solvates thereof.

In an embodiment of the present invention in the salt of formula (I) n has the value of 2.

The invention also encompasses pharmaceutical compositions comprising a therapeutically effective amount of a salt as hereinabove defined and a pharmaceutically acceptable carrier.

In an embodiment of the present invention the pharmaceutical composition further comprises a therapeutically effective amount of one or more other therapeutic agents.

It is also an embodiment of the present invention that the pharmaceutical composition is formulated for administration by inhalation.

The salts of the present invention as hereinabove defined may also be combined with one or more other therapeutic agents, in particular one or more drugs selected from the group consisting of corticosteroids, anticholinergic agents and PDE4 inhibitors.

~~The invention is also directed to a method of treating a disease or condition in a mammal associated with  $\beta$ 2 adrenergic receptor activity, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition comprising a  $\beta$ 2 adrenergic receptor agonist according to the present invention. It is of particular relevance the method applied to the treatment of a disease or condition which is a pulmonary disease, preferably asthma or chronic obstructive pulmonary disease.~~

- 7 -

The invention is also directed to the use of a salt of formula (I) in the manufacture of a medicament for the treatment of a pulmonary disease or condition in a mammal. The mammal is preferably a human being. Particularly relevant pulmonary diseases or conditions are asthma or chronic obstructive pulmonary disease.

5

The invention is also directed to a salt of formula (I) for use in the treatment of ~~a~~  $\langle \rangle$ , in a pulmonary disease or condition. The mammal is preferably a human being. Particularly relevant pulmonary diseases or conditions are asthma or chronic obstructive pulmonary disease.

10

#### General Synthetic Procedures

The salts of the invention can be prepared using the methods and procedures described herein, or using similar methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

20

Processes for preparing salts of the invention are provided as further embodiments of the invention and are illustrated by the procedures below.

25

The crystalline salts of the invention can be synthesized from 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one and from naphthalene-1,5-disulfonic acid (also known as Armstrong's Acid) or from its tetrahydrate which are commercially available from, for example, Aldrich.

30

Suitable inert diluents for this reaction include, but are not limited to, acetone, dimethylformamide, methanol, ethanol, isopropanol, isobutanol, ethyl acetate, acetic acid and the like, and mixtures thereof, optionally containing water. For example, the free base can be contacted with anhydrous naphthalene-1,5-disulfonic acid, dissolved in methanol.

Upon completion of any of the foregoing reactions, the crystalline salts can be isolated from the reaction mixture by any conventional means such as precipitation, concentration, centrifugation and the like.

- 5 It will be appreciated that while specific process conditions (i.e. reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated.

- 10 A crystalline mononapadisylate salt of the invention typically contains between about 0.8 and 1.2 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base, more typically about 1.0 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base.

- 15 A crystalline heminapadisylate salt of the invention typically contains between about 0.35 and 0.65 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base, more typically about 0.5 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base.

- 20 The molar ratios described in the methods of the invention can be readily determined by various methods available to those skilled in the art. For example, such molar ratios can be readily determined by <sup>1</sup>H NMR. Alternatively, elemental analysis and HPLC methods can be used to determine the molar ratio.

- 25 To prepare a crystalline heminapadisylate salt, the free base is typically dissolved in a solvent such as acetonitrile, dimethylformamide, methanol, ethanol, isopropanol, isobutanol, ethyl acetate, acetic acid and mixtures thereof, particularly in methanol to form a 0,10-0,12M solution which is heated to approximately 45-55°C. 0,05-0,06 mols of naphthalene-1,5-disulfonic acid tetrahydrate per liter of base solution are added to the heated solution. The mixture is then stirred for 30 minutes at reflux temperature and then  
30 cooled down to 20/25°C and stirred at this temperature for 1 additional hour. The precipitate formed is isolated by filtration, washed with an appropriate solvent such as methanol and dried for example in vacuum at 50°C.

### EXAMPLES

General. Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received.

Crystallizations test of salts of 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(*R*)-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one with a broad range of pharmaceutically acceptable acids (comprising among others fumaric, succinic, sulphuric, 1-hydroxy-2-naphthoic, L-tartaric, D-tartaric, hydrochloric, methylsulfonic, p-toluensulfonic, naphthalensulfonic, L-mandelic, D,L-mandelic, citric, 1*S*-camphor-10-sulfonic, L-malic, L-aspartic, L-pirolglutamic and 1,5-disulfonic acids) in a range of different pharmaceutically acceptable solvents (including among others acetone, acetonitrile, ethyl acetate, isobutyl acetate, 2-butanol, chloroform, dichloromethane, dioxane, dimethylformamide, ethanol, water, isopropanol, methyl ethyl ketone, methanol, tetrahydrofuran and toluene) have been undertaken.

Only a few of these tests have yielded crystalline salts. From these crystalline salts only the napadisylate salts were neither hygroscopic nor deliquescent and had a relatively high melting point allowing them to be micronized and to have a long term stability.

A particularly good method to prepare a 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(*R*)-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one heminaadisylate salt comprises dissolving 14,4 mmols of free base in 134 ml of methanol to form a 1,075 M solution which is heated to approximately 50°C. Then, 7.74 mmols of naphthalene-1,5-disulfonic acid tetrahydrate are added to the heated solution. The mixture is then stirred for 30 minutes at reflux temperature and then cooled down to 20/25°C and stirred at this temperature for 1 additional hour. The precipitate formed is isolated by filtration, washed with methanol and dried in vacuum at 50°C.

X-Ray Powder Diffraction (XRPD) analysis was performed on a Panalytical X-ray powder diffractometer, model X'Pert PRO MPD. The method runs from 2 to 50 degrees 2-Theta with a 0.017 degree 2-Theta step size and a 300 second collection time at each step using an X'celerator detector.

Figure 1 shows an XRPD pattern of the salt 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy) hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate, which confirms the crystallinity of the sample.

5

The differential scanning calorimetry (DSC) analysis was obtained using a DSC-821 Mettler-Toledo, serial number 5117423874. Samples were weighed into an aluminium pan, an aluminium lid placed on top of the sample and compressed with a brass rod. Samples were equilibrated at 30°C and heated at 10°C / min to 300°C. The instrument

10

was calibrated using indium and zinc standards.

Figure 2 shows a DSC pattern of the salt 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy)hexyl-amino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate. The sample exhibits an endotherm with an onset of around 206°C and there are no changes prior to

15

the melting point range. This indicates that the sample does not convert into any other polymorphs and does not suffer any decomposition, confirming thus its high stability

The thermogravimetric (TGA) analysis was obtained using a TGA-SDTA-851 Mettler-Toledo, serial number 5118408555. Samples were placed into a tared aluminium pan and

20

then positioned on a platinum crucible. Samples were heated from 30°C at 10°C / min to 350°C. The instrument was calibrated using indium and aluminium standards.

Figure 3 shows a TGA pattern of 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate. The sample exhibits a

25

weight loss of 3.1% w/w from approximately 200°C to 220°C due to the decomposition of the sample. Prior to 200°C, and in particular at the temperature range of 80-100°C, the sample does not exhibit any change. This indicates that there is no solvent / water release, confirming thus the lack of hygroscopicity of the sample.

### 30 **Pharmaceutical Compositions**

Pharmaceutical compositions according to the present invention comprise a therapeutically effective amount of a napadisylate salt of 5-(2-([6-(2,2-difluoro-2-phenylethoxy) hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one or an

enantiomer or pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier.

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the salt of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred.

Each capsule or cartridge may generally contain between 2 $\mu$ g and 150  $\mu$ g of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

Effective doses are normally in the range of 1-2000  $\mu$ g of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

For inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal

force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients.

- 5 Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has  
10 been reported (e. g. Nielsen et al, 1997).

Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with  
15 capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

- 20 Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose  
25 system, including the technique used to transport the strip and open the blister pockets.

Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually  
30 from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e. g. EP0069715) or disks (e. g. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (e. g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e. g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices  
35 have measuring plungers with a local or circumferential recess to displace a certain

- 13 -

volume of powder from the container to a delivery chamber or an air conduit (e. g. EP 0505321, WO 92/04068 and WO 92/04928), or measuring slides such as the Novolizer SD2FL (ex. Sofotec) which is described in the following patent applications: WO 97/000703, WO 03/000325 and WO 03/061742.

5

Reproducible dose measuring is one of the major concerns for multi dose inhaler devices. The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity. For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

10

Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

15

Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose devices, powder adhesion onto the inner walls of the air conduits and the de-agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (e. g. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even more strict.

20

25

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 $\mu$ , preferably 2-5 $\mu$ . Particles having a size above 20 $\mu$  are generally too large when inhaled to reach the small airways. To achieve these particle sizes, the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

30

35

Apart from applications through dry powder inhalers the compositions of the invention can also be administered in aerosols which operate via propellant gases or by means of so-called atomisers, via which solutions of pharmacologically-active substances can be  
5 sprayed under high pressure so that a mist of inhalable particles results. Such atomisers are described, for example, in WO 91/14468 and WO 97/12687.

Achieving high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry  
10 powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient such as lactose or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, preferably crystalline alpha lactose monohydrate.  
15 Pressurized aerosol compositions will generally be filled into canisters fitted with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e. g. a fluorocarbon polymer as described in W096/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

20 Each dosage unit contains suitably from 1  $\mu\text{g}$  to 100  $\mu\text{g}$ , and preferably from 5  $\mu\text{g}$  to 50  $\mu\text{g}$  of a  $\beta$ 2-agonist according to the invention.

The compositions of the invention can optionally comprise a therapeutically effective amount of one or more other therapeutic agents which are known to be useful in the  
25 treatment of respiratory disorders, such as PDE4 inhibitors, corticosteroids and/or anticholinergics.

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment,  
30 and the particular disorder or disease being treated.

The active ingredients may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity. Preferably, the active ingredients are administered once or twice a day, most preferably once a day.  
35

- 15 -

Examples of suitable PDE4 inhibitors that can be combined with  $\beta$ 2-agonists are denbutylline, rolipram, cipamfylline, arofylline, filaminast, piclamilast, m sopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, oglemilast, apremilast, 6-[2-(3,4-diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid (tetomilast), (R)-(+)-4-[2-(3-

5 Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine, N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide, N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-

10 tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide, 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride, 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-

15 difluoromethoxyphenyl)cyclohexan-1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the salts claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692.

Examples of suitable corticosteroids and glucocorticoids that can be combined with  $\beta$ 2-agonists are prednisolone, methylprednisolone, dexamethasone, dexamethasone

20 cipeclate, naflcort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate,

25 rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RPR-106541, deprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone

30 sodium succinate, prednisolone sodium phosphate and hydrocortisone probutate.

Examples of suitable M3 antagonists (anticholinergics) that can be combined with  $\beta$ 2-agonists are tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, revatropate, espatropate, 3-[2-Hydroxy-2,2-bis(2-

35 thienyl)acetoxyl-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts (in particular

acridinium salts, more preferably acridinium bromide), 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, 2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxylic acid endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester salts (DAU-5884), 3-(4-Benzylpiperazin-1-yl)-1-cyclobutyl-1-hydroxy-1-phenylpropan-2-one (NPC-14695), N-[1-  
5 (6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2(R)-[3,3-difluoro-1(R)-cyclopentyl]-2-hydroxy-2-phenylacetamide (J-104135), 2(R)-Cyclopentyl-2-hydroxy-N-[1-[4(S)-methylhexyl]piperidin-4-yl]-2-phenylacetamide (J-106366), 2(R)-Cyclopentyl-2-hydroxy-N-[1-(4-methyl-3-pentenyl)-4-piperidinyl]-2-phenylacetamide (J-104129), 1-[4-(2-Aminoethyl)piperidin-1-yl]-2(R)-[3,3-difluorocyclopent-1(R)-yl]-2-hydroxy-2-phenylethan-1-  
10 one (Banyu-280634), N-[N-[2-[N-[1-(Cyclohexylmethyl)piperidin-3(R)-ylmethyl]carbamoyl]ethyl]carbamoylmethyl]-3,3,3-triphenylpropionamide (Banyu CPTP), 2(R)-Cyclopentyl-2-hydroxy-2-phenylacetic acid 4-(3-azabicyclo[3.1.0]hex-3-yl)-2-butyryl ester (Ranbaxy 364057), UCB-101333, Merck's OrM3, 7-endo-(2-hydroxy-2,2-diphenylacetoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0(2,4)]nonane salts, 7-(2,2-diphenylpropionyloxy)-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0\*2,4\*]nonane salts, 7-  
15 hydroxy-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0\*2,4\*]nonane 9-methyl-9H-fluorene-9-carboxylic acid ester salts, all of them optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally in the form of their pharmacologically-compatible acid addition salts. Among the salts chlorides, bromides,  
20 iodides and methanesulphonates are preferred.

Particularly preferred pharmaceutical composition according to the invention comprise a salt of formula (I) and a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of mometasone furoate,  
25 ciclesonide, budesonide, fluticasone propionate, fluticasone furoate, tiotropium salts, glycopyrronium salts, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts (in particular acridinium salts, preferably acridinium bromide), 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, rolipram, roflumilast, cilomilast and the compounds claimed in the PCT patent  
30 applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692

Thus, in one aspect of the invention, the composition comprises a salt of formula (I) and a corticosteroid. Particularly preferred corticosteroids are those selected from the group

- 17 -

consisting of mometasone furoate, ciclesonide, budesonide, fluticasone furoate and fluticasone propionate.

5 In another aspect of the invention, the composition comprises a salt of formula (I) and an anticholinergic agent. Particularly preferred anticholinergic agents are those selected from the group consisting of tiotropium salts, glycopyrronium salts, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts and 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts. The composition may further comprise a corticosteroid selected from the group consisting of  
10 mometasone furoate, ciclesonide, budesonide, fluticasone furoate and fluticasone propionate.

In a still other aspect of the invention, the composition comprises a salt of formula (I) and a PDE4 inhibitor. Particularly preferred PDE4 inhibitors are those selected from the  
15 group consisting of rolipram, roflumilast, cilomilast and the compounds claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692. The composition may further comprise a corticosteroid selected from the group consisting of mometasone furoate, ciclesonide, budesonide, fluticasone furoate and fluticasone propionate. In addition to the salt of the  
20 invention and to the PDE4 inhibitor, the composition may further comprise an anticholinergic agent selected from the group consisting of tiotropium salts, glycopyrronium salts, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts and 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts.

25 In a particularly preferred embodiment of the present invention, the composition comprises a salt of formula (I) and a therapeutically effective amount of a 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts. Optionally, the composition further comprises a corticosteroid and/or a PDE4 inhibitor.

30 In another particularly preferred embodiment of the present invention, the composition comprises a salt of formula (I) and a therapeutically effective amount of mometasone furoate. Optionally, the composition further comprises an anticholinergic and/or a PDE4 inhibitor.

35

- 18 -

In yet another embodiment of the invention, the composition comprises salt of formula (I), a corticosteroid, an anticholinergic agent and a PDE4 inhibitor.

The salts of formula (I) and the combinations of the invention may be used in the treatment of respiratory diseases, wherein the use of bronchodilating agents is expected to have a beneficial effect, for example asthma, acute or chronic bronchitis, emphysema, or Chronic Obstructive Pulmonary Disease (COPD).

The active compounds and the salts in the combination, i.e. the  $\beta$ 2-agonist of the invention and the PDE4 inhibitors, corticosteroids or glucocorticoids and/or anticholinergics may be administered together in the same pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

It is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one or two actives could be taken in the morning and the other (s) later in the day. Or in another scenario, one or two actives could be taken twice daily and the other (s) once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably at least two, and more preferably all, of the actives would be taken together at the same time. Preferably, at least two, and more preferably all actives would be administered as an admixture.

The active substance compositions according to the invention are preferably administered in the form of compositions for inhalation delivered with the help of inhalers, especially dry powder inhalers; however, any other form of topical, parenteral or oral application is possible. Here, the application of inhaled compositions embodies the preferred application form, especially in the therapy of obstructive lung diseases or for the treatment of asthma.

Additional suitable carriers for formulations of the active salts of the present invention can be found in Remington: The Science and Practice of Pharmacy, 20th Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2000. The following non-limiting examples illustrate representative pharmaceutical compositions of the invention.

~~The invention further encompasses a method of treating a pulmonary disease or condition, such as asthma or chronic obstructive pulmonary disease in a mammal associated with  $\beta$ 2 adrenergic receptor activity, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition as~~

5 described above.

In particular the method of treating a pulmonary disease or condition comprises administering to the mammal, a therapeutically effective amount of a napadisylate salt of a compound of formula (I) and a therapeutically effective amount of one or more other

10 ~~therapeutic agents, such as a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor~~

Formulation Example 1 (Gelatin cartridge for inhalation)

| Ingredient                                                                                                                   | Amount |
|------------------------------------------------------------------------------------------------------------------------------|--------|
| 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one, napadisylate (micronized) | 0,2 mg |
| Lactose                                                                                                                      | 25 mg  |

15 Formulation Example 2 (Formulation for inhalation with a DPI)

| Ingredient                                                                                                                    | Amount  |
|-------------------------------------------------------------------------------------------------------------------------------|---------|
| 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one, napadisylate (micronized) | 15 mg   |
| Lactose                                                                                                                       | 3000 mg |

## Formulation Example 3 (Formulation for inhalation with a DPI)

| Ingredient                                                                                                                    | Amount  |
|-------------------------------------------------------------------------------------------------------------------------------|---------|
| 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one, napadisylate (micronized) | 15 mg   |
| 3(R)-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide                           | 100 mg  |
| Lactose                                                                                                                       | 3000 mg |

## Formulation Example 4 (Formulation for inhalation with a DPI)

5

| Ingredient                                                                                                                    | Amount  |
|-------------------------------------------------------------------------------------------------------------------------------|---------|
| 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one, napadisylate (micronized) | 15 mg   |
| Mometasone furoate                                                                                                            | 400 mg  |
| Lactose                                                                                                                       | 3000 mg |

## Formulation Example 5 (Formulation for inhalation with a DPI)

| Ingredient                                               | Amount |
|----------------------------------------------------------|--------|
| 5-(2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1(R)- | 15 mg  |

- 21 -

|                                                                                                     |         |
|-----------------------------------------------------------------------------------------------------|---------|
| hydroxy-ethyl)-8-hydroxyquinolin-2(1 <i>H</i> )-one, napadisylate (micronized)                      |         |
| 3(R)-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide | 100 mg  |
| Mometasone furoate                                                                                  | 400 mg  |
| Lactose                                                                                             | 3000 mg |

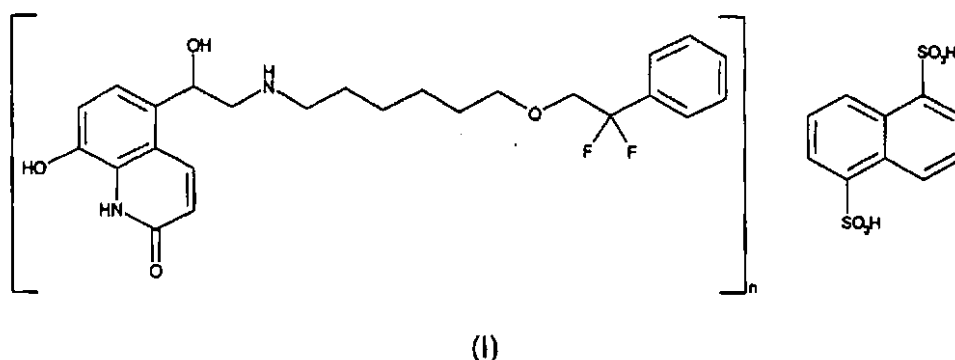
## Formulation Example 6 (Formulation for a MDI)

| Ingredient                                                                                                                             | Amount         |
|----------------------------------------------------------------------------------------------------------------------------------------|----------------|
| 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1(R)-hydroxy-ethyl)-8-hydroxyquinolin-2(1 <i>H</i> )-one, napadisylate (micronized) | 10 g           |
| 1,1,1,2,3,3,3-heptafluoro-n-propane                                                                                                    | q.s. to 200 ml |

## CLAIMS

1. A crystalline mononapadisylate and/or heminapadisylate salt of 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one and  
 5 pharmaceutically acceptable solvates thereof.

2. A salt according to claim 1, which has the formula (I):



- 10 wherein *n* has a value of 1 or 2

and pharmaceutically acceptable solvates thereof.

3. A salt according to claim 2 wherein *n* has a value of 2.

15

4. A salt according to claim 1 selected from the group consisting of:

- (*R,S*) 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, napadisylate  
 20 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(*R*)-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, napadisylate  
 (*R,S*) 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate, and  
 25 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(*R*)-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate

and pharmaceutically acceptable solvates thereof.

5. A salt according to claim 4 selected from the group consisting of:

(*R,S*) 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate  
5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(*R*)-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate

5

and pharmaceutically acceptable solvates thereof.

6. A salt according to claim 5 which is 5-(2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(*R*)-hydroxy-ethyl)-8-hydroxyquinolin-2(1*H*)-one, heminapadisylate or a pharmaceutically acceptable solvate thereof.

10

7. A pharmaceutical composition comprising a therapeutically effective amount of a salt according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

15

8. The pharmaceutical composition according to claim 7, wherein the composition is formulated for administration by inhalation.

9. The pharmaceutical composition of claim 7 or 8, wherein the composition further comprises a therapeutically effective amount of one or more other therapeutic agent.

20

10. The pharmaceutical composition of claim 9 wherein the other therapeutic agent is a corticosteroid, an anticholinergic agent, and/or a PDE4 inhibitor.

11. The pharmaceutical composition of claim 10 wherein the other therapeutic agent is a corticosteroid selected from the group consisting of prednisolone, methylprednisolone, dexamethasone, dexamethasone cipeclate, naflacort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RPR-106541, deprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate,

30

35

triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate and hydrocortisone probutate.

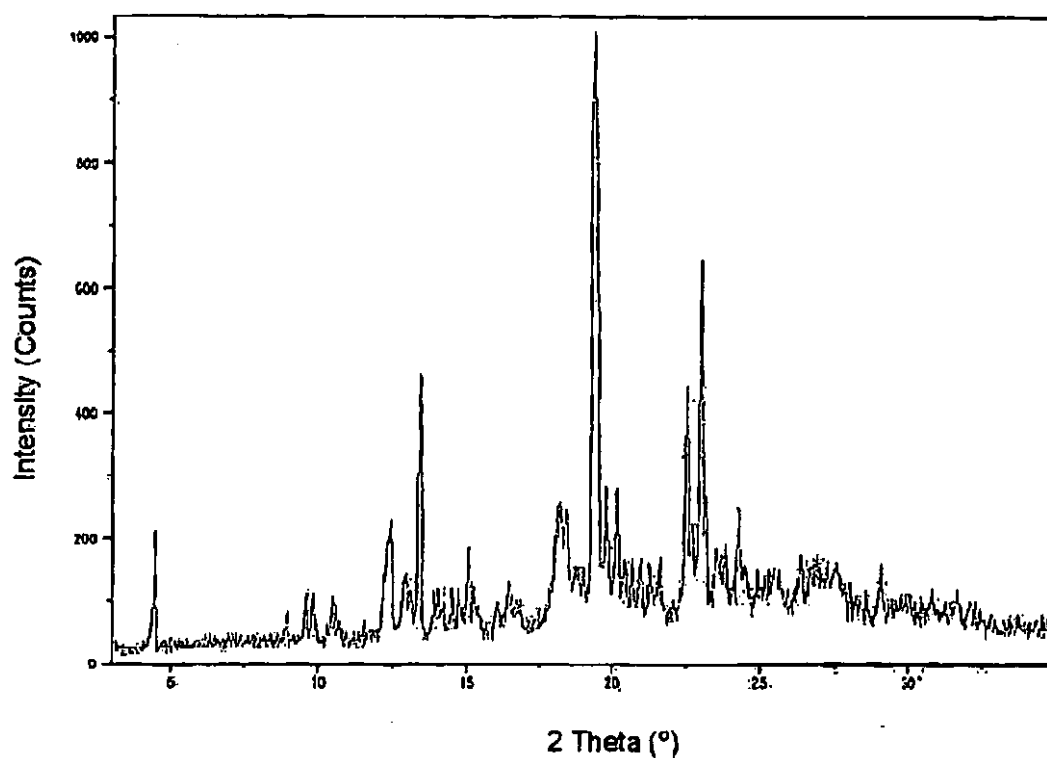
- 5 12. The pharmaceutical composition of claim 10 wherein the other therapeutic agent is an anticholinergic agent selected from the group consisting of tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, revatropate, espatropate, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-  
10 azoniabicyclo[2.2.2]octane salts, 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, 2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxylic acid endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester salts (DAU-5884), 3-(4-Benzylpiperazin-1-yl)-1-cyclobutyl-1-hydroxy-1-phenylpropan-2-one (NPC-14695), N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2(R)-[3,3-difluoro-1(R)-cyclopentyl]-2-hydroxy-2-phenylacetamide (J-104135), 2(R)-Cyclopentyl-2-hydroxy-N-[1-[4(S)-methylhexyl]piperidin-4-yl]-2-  
15 phenylacetamide (J-106366), 2(R)-Cyclopentyl-2-hydroxy-N-[1-(4-methyl-3-pentenyl)-4-piperidiny]-2-phenylacetamide (J-104129), 1-[4-(2-Aminoethyl)piperidin-1-yl]-2(R)-[3,3-difluorocyclopent-1(R)-yl]-2-hydroxy-2-phenylethan-1-one (Banyu-280634), N-[N-[2-[N-[1-(Cyclohexylmethyl)piperidin-3(R)-ylmethyl]carbonyl]ethyl]carbonylmethyl]-3,3,3-triphenylpropionamide (Banyu CPTP), 2(R)-Cyclopentyl-2-hydroxy-2-phenylacetic acid 4-  
20 (3-azabicyclo[3.1.0]hex-3-yl)-2-butynyl ester (Ranbaxy 364057), UCB-101333, Merck's OrM3, 7-endo-(2-hydroxy-2,2-diphenylacetoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0(2,4)]nonane salts, 7-(2,2-diphenylpropionyloxy)-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0\*2,4\*]nonane salts, 7-hydroxy-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0\*2,4\*]nonane 9-methyl-9H-fluorene-9-carboxylic acid ester salts, all  
25 of them optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally in the form of their pharmacologically-compatible acid addition salts.

13. The pharmaceutical composition of claim 10 wherein the other therapeutic agent is a  
30 PDE4 inhibitor selected from the group consisting of denbufylline, rolipram, cipamfylline, arofylline, filaminast, piclamilast, mesopram, drotaverine hydrochloride, liramilast, roflumilast, cilomilast, oglemilast, apremilast, 6-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid (tetomilast), (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-  
35 5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-

- (trifluoromethyl)adenine, N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide, N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide, 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride, 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, and ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557).
- 10 14. The pharmaceutical composition according to any one of claims 9 to 13 wherein the other therapeutic agent is selected from the group consisting of mometasone furoate, ciclesonide, budesonide, fluticasone propionate, fluticasone furoate, tiotropium salts, glycopyrronium salts, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts, 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, rolipram, roflumilast and cilomilast.
- 15 15. A combination comprising a salt as defined in any one of claims 1 to 6 and one or more other therapeutic agents, as defined in any one of claims 9 to 14.
- 20 16. A salt according to any one of claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 14, for use in the treatment of asthma or chronic obstructive pulmonary disease in a mammal.
- 25 17. A salt or pharmaceutical composition <sup>Y < ① ></sup> according to claim 16, wherein the salt or pharmaceutical composition is coadministered with one or more other therapeutic agents, as defined in any one of claims 9 to 14.

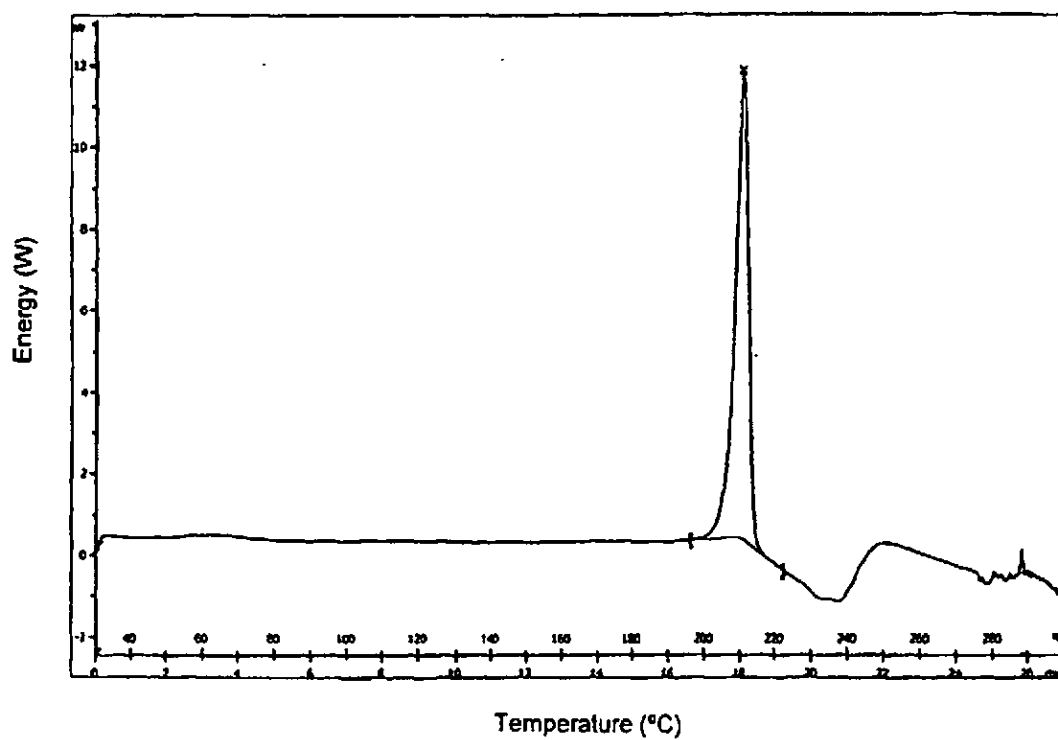
① for use in the treatment of asthma or chronic obstructive pulmonary disease

Figure 1: X-Ray Powder Diffraction (XRPD) pattern of 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate.



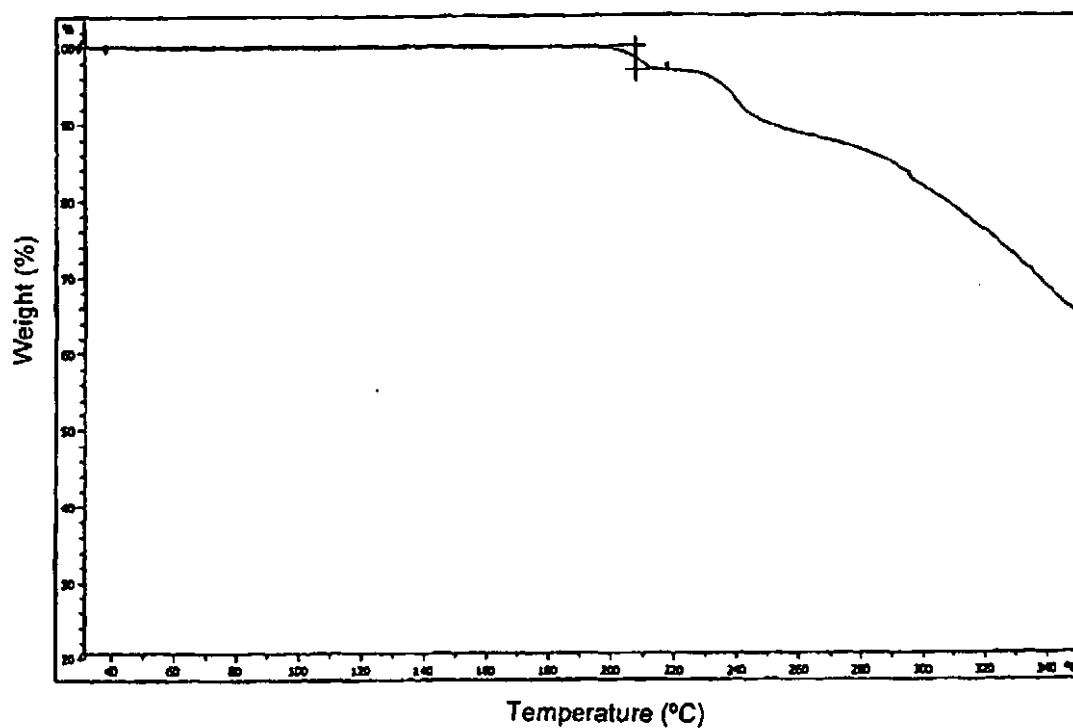
SUBSTITUTE SHEET (RULE 26)

Figure 2: DSC pattern of 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy) hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate.



SUBSTITUTE SHEET (RULE 26)

Figure 3: TGA pattern of 5-(-2-(6-(2,2-Difluoro-2-phenylethoxy)hexylamino)-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one heminapadisylate.



SUBSTITUTE SHEET (RULE 26)